Reitstötter, Kinzebach & Partner (GbR)

Patentanwälte

Dr. Werner Kinzebach
Dr. Peter Riedl
Dr. Georg Schweiger
Dr. J. Uwe Müller
Dr. Wolfgang Thalhammer
Dr. Michael Pohl
Dr. Thomas Wolter
Andreas Rabe
Dr. Jens Wortmann
Prof. Dr. Dr. Reitstötter (1982)

Zugelassene Vertreter beim
Europäischen Patentamt
European Patent Attorneys
Telefon: +49(0)89 99 83 97 - 0
Telefax: +49(0)89 98 73 04
Sternwartstr. 4, D-81679 München
email: office@kinzebach.de

Reitstötter, Kinzebach & Partner
Postfach 86 06 49, D-81633 München

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Abbott Laboratories (Bermuda) Ltd.

In response to the Written Opinion under Rule 66 PCT dated August 2, 2004:

Attached we submit a modified set of claims (claims 1-23) to replace the claims presently on file. It is requested to continue examination proceedings on the basis of said new claims.

As to the amended claims:

Claim 8 was amended in view of the clarity rejection raised by the examiner.

Claim 6 is now directed to a formulation containing a human antibody.

As to the clarity rejection:

The Written Opinion sets forth that claims 1 and 8 lack clarity. Claim 8 has been amended to include the phrase "with the following characteristics" to reflect that the antibody requires all of the listed characteristics. Thus, the rejection of claim 8 for lack of clarity is overcome.

The Written Opinion also states that claim 1 (and dependent claims 2-12) does not contain the essential technical features of the invention. Applicant respectfully disagrees with this assessment. The invention is directed to a stable, aqueous pharmaceutical formulation comprising an antibody. Claim 1 is directed to a pharmaceutical formulation selected from the group consisting of (a) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months; (b) an aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months in the liquid state; (c) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 which maintains stability following at least 3 freeze/thaw cycles of the formulation; and (d) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between 4 and 8 and having enhanced stability of at least 12 months at a temperature of 2 - 8°C. In contrast to the assertions set forth in the Written Opinion, each of the formulations recited in claim 1 contains an essential technical feature *of* the invention. Parts (a) and (b) of claim 1 require that ***the aqueous pharmaceutical*** formulation have ***a shelf life of at least 18 months***. Parts (c) and (d) of claim 1 require that the ***aqueous pharmaceutical*** formulation have ***stability following at least 3 freeze/thaw cycles of the formulation***. Furthermore, claim 1 also requires the pharmaceutical formulation to comprise an antibody. Thus, each of the elements of claim 1 (and dependent claims 2-12) recites the essential features of the invention, i.e., ***a stable, aqueous pharmaceutical formulation comprising an antibody.***

As to the novelty rejections:

Applicant gratefully acknowledges that claims 6-12, 16, and 20-23 have been indicated as novel over the prior art.

With regard to the alleged lack of novelty of claims 1, 3-5, 13-15, and 17-19 over D1 (Corbo *et al.*, U.S. Patent No. 6,024,938) and claims 1, 3 -5, 13, and 14 over D2 (Okada *et al.*, EP Patent Appln. No. EP 1 174 148), we would like to add the following comments:

The Written Opinion sets forth that "D1 discloses a pharmaceutical formulation comprising 1 mg/ml SHNH-IgG, 0.9% saline, 1-25% maltose (can be replaced by mannitol; both are drying protectants), polysorbate 80 (0,01%, Tween), citrate buffer

(20 nM) with pH 5.2." The Written Opinion also sets forth that "the formulation is lyophilized and may be stored stably for extended periods of time." The Written Opinion contends that claims 1, 3-5, 13-15 and 17-19 lack novelty as being anticipated by D1. Applicant respectfully disagrees.

Applicant submits that claims 1, 3-5, 13-15, and 17-19 are novel over D1. The instant claims are directed to a stable, aqueous pharmaceutical formulation comprising an antibody, wherein the formulation has a shelf life of at least 18 months or stability following at least 3 freeze/thaw cycles of the formulation. The present invention is also directed to an aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate with a pH of about 4 to 8, in amounts sufficient to formulate an antibody for therapeutic use at a concentration of greater than about 45 mg/ml. Claim 17 of the present invention is directed to a liquid aqueous pharmaceutical formulation comprising 1-150 mg/ml of antibody; 5-20 mg/ml of mannitol; 0.1-10 mg/ml of Tween-80; and a buffer system comprising citrate and/or phosphate, with a pH of 4 to 8.

D1 teaches imaging agent compositions and methods of making said compositions. The term "imaging agent" as defined by D1 comprises "a conjugate formed between 'targeting molecule'....and a 'linker'" (see col. 6, lines 16-22). In the examples provided by reference D1, including the example referenced in the Written Opinion (see col. 9, lines 4-29), all of the imaging agent compositions comprise a targeting molecule, such as an antibody or chemotactic peptide, ***conjugated to a linker***, such as diethylenetriamineepentaacetic acid (DTPA) or succinimidyl 6-hydrazinium nicotinate hydrochloride (SHNH). D1 also teaches ***lyophilization*** of the imaging agent composition to ***increase the shelf life*** of the conjugated targeting molecule (see col. 11, last paragraph, referenced in Written Opinion). Finally, reference D1 teaches that the preferred concentration of the imaging agent in the composition is 1.0 mg/ml (see col. 8, lines 49-51).

In contrast to claims 1, 3-5, 13-15, and 17-19 which require that the pharmaceutical formulation comprise ***an antibody***, D1 teaches an imaging agent composition which contains a targeting molecule ***conjugated to a linker***. The instant invention provides an improved pharmaceutical formulation comprising an antibody in a stable aqueous environment without the need for modifications to the antibody. D1 requires an additional agent, *i.e.*, a linker, to be conjugated to the antibody or targeting molecule. In addition, unlike the compositions taught in D1, Applicant's invention does not require lyophilization for increased stability. Claims 1, 3-5 and 17-19 of the instant invention require that the pharmaceutical formulation with improved shelf life or improved freeze/thaw stability be in a ***liquid state***. Finally, D1 teaches that the

preferred imaging agent concentration is 1.0 mg/ml and does not teach or suggest Applicant's improved pharmaceutical formulation comprising a high protein concentration. Claims 13-15 require that the pharmaceutical formulation comprise a buffer system in amounts sufficient to formulate an antibody at a ***concentration of greater than about 45 mg/ml.***

The Written Opinion also sets forth that claims 1, 3-5, 13, and 14 lack novelty as being anticipated by reference D2. The Written Opinion states that, "D2 discloses a Fab fragment preparation comprising 1) 0,01-10 mg/ml Fab fragment, 2) 0.01-50% sucrose and/or mannitol, 3) 0.0001-0.1% of anionic surface active agent...4) 1-500 mM of a buffer ... 4) having pH 4-6". The Written Opinion contends that claims 1, 3-5, 13, and 14 lack novelty as being anticipated by D2. Applicant respectfully disagrees.

Applicant submits that claims 1, 3-5, 13, and 14 are novel over D2. The compositions described by D2 are specific to humanized monoclonal antibody ***fragments***, specifically Fab fragments. D2 does not teach or suggest compositions comprising a complete antibody. Furthermore, D2 teaches that the preferred antibody fragment concentration is 0,1 to 8 mg/ml (see page 3, line 10), whereas claims 13 and 14 require that the pharmaceutical formulation comprise a buffer system in amounts sufficient to formulate an antibody at a ***concentration of greater than about 45 mg/ml.***

Accordingly, Applicant respectfully submits that claims 1, 3-5, 13-15, and 17-19 are novel over D1 and that claims 1, 3-5, 13, and 14 are novel over D2. None of the references teach or suggest a stable, aqueous pharmaceutical formulation comprising an antibody, wherein the formulation has a shelf life of at least 18 months or stability following at least 3 freeze/thaw cycles of the formulation. In addition, none of the references teach or suggest an aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate with a pH of about 4 to 8, in amounts sufficient to formulate an antibody for therapeutic use at a concentration of greater than about 45 mg/ml. Finally, neither D1 nor D2 teach or suggest a liquid aqueous pharmaceutical formulation comprising 1-150 mg/ml of antibody; 5-20 mg/ml of mannitol; 0.1-10 mg/ml of Tween-80; and a buffer system comprising citrate and/or phosphate, with a pH of 4 to 8.

As to the inventive step rejections

Claims 1-5 and 13-15 are assumed to be inventive over the prior art, as they have not been indicated as lacking inventive step in the Written Opinion.

With regard to the alleged lack of inventive step of claims 6-12 and 16-23 in view of references D1, D2, or D3 (Salfeld *et al.*, U.S. Patent No. 6,090,382), we would like to add the following comments:

In the statement set forth in the Written Opinion, it is alleged that claims 6-12 and 16-23 lack inventive step under PCT Article 33(3) as being obvious over reference D3. The Written Opinion sets forth that "[t]he difference between the subject matter of claims 6-12... as well as claims 16-23 and D3 is that a specific stable aqueous pharmaceutical formulation with an extended shelf life for an anti-TNF-alpha Ab is provided." The Written Opinion further states that "[t]he technical problem is to provide a specific stable aqueous pharmaceutical formulation with an extended shelf life for an anti-TNF-alpha Ab." Applicant respectfully disagrees with the contention that claims 6-12 and 16-23 are obvious in view of D3.

Applicant submits that claims 6-12 and 16-23 are inventive over D3. Applicant provides an improved aqueous pharmaceutical formulation with improved characteristics, *e.g.*, improved stability and/or high protein concentration as compared to art recognized formulations. As discussed above, the instant claims are directed to a stable, aqueous pharmaceutical formulation comprising an antibody, ***wherein the formulation has a shelf life of at least 18 months or stability following at least 3 freeze/thaw cycles of the formulation.*** The present invention is also directed to an aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system in amounts sufficient to formulate an antibody for therapeutic use at a concentration of ***greater than about 45 mg/ml.*** Claim 17 of the present invention is directed to a liquid aqueous pharmaceutical formulation comprising 1-150 mg/ml of antibody; 5-20 mg/ml of mannitol; 0.1-10 mg/ml of Tween-80; and a buffer system comprising citrate and/or phosphate, with a pH of 4 to 8. The present invention also describes said pharmaceutical formulations, wherein the antibody is D2E7.

Salfeld *et al.* teach fully human neutralizing anti-TNFα antibodies with high affinity for TNFα. The Written Opinion asserts that "D3 mentions that many methods for the preparation of such formulations are patented or generally known to those skilled in the art," and notes references which are cited in D3. Applicant submits that D3 does not teach or suggest all of the elements of the pending claims alone or in combination with the references cited therein. Claims 6-12 specify pharmaceutical formulations with ***improved stability.*** Claim 16 depends from claim 13 which requires that the aqueous pharmaceutical formulation comprise a buffer system in amounts sufficient to formulate an antibody *at a* ***concentration of greater than***

about 45 mg/ml. As acknowledged by the Written Opinion, "[t]he technical problem is to provide a specific stable aqueous pharmaceutical formulation with an extended shelf life". Applicant submits that an aqueous pharmaceutical formulation with improved concentration or improved stability characteristics (characteristics acknowledged by the Written Opinion as problems in the art) are required elements of claims 6-12 and 16-23. Furthermore, claims 17-23 require specific ingredients, which Applicant demonstrates through a working example in the instant specification results in a pharmaceutical formulation with both improved shelf life and the ability to dissolve high concentrations of proteins (see examples 1 and 2 at pages 28-30 of instant specification). Based on the teachings of D3 alone or in combination with methods known in the art, Applicant submits that it is not obvious to one of ordinary skill in the art to combine the specific ingredients of claim 17 to provide a pharmaceutical formulation with improved stability and/or a high protein concentration.

The Written Opinion also alleges that claims 6-12 and 16-23 lack inventive step under PCT Article 33(3) as being obvious over references D1 or D2. The Written Opinion sets forth that "[c]ombining the teachings of the closest prior art with D1 (or D2), the skilled person has clear indications for substances to be used in such high stability formulations, i.e. a polyol, a surfactant and a buffer system comprising citrate and/or phosphate with a pH 4-6." The Written Opinion further states that "[a]pplying trivial routine testing it would be easy for the skilled person to determine the optimal formulation for the desired amounts of a given Ab." Applicant respectfully disagrees.

Absent the teachings of the invention, there is nothing in the cited references to suggest to one of ordinary skill in the art how to arrive at a pharmaceutical formation comprising an antibody, wherein the formulation has improved stability and the ability to retain high protein concentrations. The above discussion of D1 and D2 with regard to novelty is reiterated here. D1 and D2 each teach compositions comprising a ***modified antibody,*** wherein the antibody is either conjugated to a linker or is an antibody fragment, respectively. One of ordinary skill in the art would recognize that such modifications would have a substantial impact on the process of making a pharmaceutical formulation, and, therefore, would not rely on either D1 or D2 to arrive at the claimed invention. Furthermore, Applicant submits that D1 and D2 each teach against the claimed invention, as one of ordinary skill would be lead to believe that modifications to an antibody are necessary to achieve a soluble composition.

Applicant submits that neither D1 nor D2 alone or in combination teaches or suggests all of the elements of the pending claims, specifically pharmaceutical formulations comprising an ***antibody with improved stability and/or a high protein***

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concentration. Claims 6-12 and 17-23 further require that the pharmaceutical formulation be in ***liquid form.*** D1 teaches compositions comprising ***conjugated testing agents*** at a ***preferred low concentration,*** wherein stability is attained through ***lyophilization.*** D2 teaches compositions comprising antibody ***fragments*** at a ***preferred low concentration.*** Thus, neither D1 nor D2 alone or in combination puts the ordinarily skilled artisan in possession of the invention as claimed.

Accordingly, Applicant respectfully submits that claims 6-12 and 16-23 each have inventive step over the methods and compositions described in D1, D2, and D3 either alone or in combination with one another.

Further remarks

Regarding the allegedly "vague statements" of the instant specification described in section 4.1 of the Written Opinion, Applicant submits that the statements referred to at page 28, lines 1-2 and page 31, lines 25-28 are included to point out that the working examples of the specification are not meant to limit the invention and that equivalent compositions and methods are encompassed as well.

Regarding the Written Opinion's assertion that the term "about" introduces "ambiguity" in the claims and the specification, Applicant asserts that the term "about" is not ambiguous but would be recognized by one of ordinary skill in the art to mean equivalent amounts of ingredients recited in the pharmaceutical formulation of the invention. For example, in the specification Applicant refers to a buffer system at page 17, lines 35-36, wherein the amount of citric acid is described as "about 1.3 mg/ml of citric acid (*e.g.*, 1.305 mg/ml)." By using the word "about," Applicant intends to include amounts "reasonably close to" the recited amount.

(Georg Schweiger)

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Encl.:
New claims 1-23

Claims (Amended)

~~What is claimed is:~~

1. A pharmaceutical formulation selected from the group consisting of:

(a) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months;

(b) an aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months in the liquid state;

(c) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 which maintains stability following at least 3 freeze/thaw cycles of the formulation; and

(d) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between 4 and 8 and having enhanced stability of at least 12 months at a temperature of 2 - 8°C.

2. The formulation of claim 1, wherein the antibody is directed to TNFα.

3. The formulation of claim 1, wherein the concentration of the antibody is between about 1-150 mg/ml.

4. The formulation of claim 1, wherein the concentration of the antibody is about 50 mg/ml.

5. The formulation of claim 1, which further is suitable for single use subcutaneous injection.

6. The formulation of claim 1, wherein the antibody is ~~an~~ a human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a K_d of 1 x 10^{-}

8 M or less and a K_{off} rate constant of 1×10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less.

7. The formulation of claim 6, wherein the antibody, or antigen-binding portion thereof, is a recombinant antibody, or antigen-binding portion thereof.

8. The formulation of claim 1, wherein the antibody is ~~an the~~ a human antibody, or antigen-binding portion, thereof ~~which~~ with the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

9. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

10. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, neutralizes the activity of human TNFα, chimpanzee TNFα and at least one additional primate TNFα selected from the group consisting of baboon TNFα, marmoset TNFα, cynomolgus TNFα and rhesus TNFα.

11. The formulation of claim 1, wherein the antibody, or an antigen-binding portion thereof, also neutralizes the activity of mouse TNFα and/or pig TNFα.

12. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, binds human TNFα and is the antibody D2E7 or an antigen binding portion thereof.

13. An aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate with a pH of about 4 to 8, in amounts sufficient to formulate an antibody for therapeutic use at a concentration of greater than about 45 mg/ml.

14. The composition of claim 13, wherein the polyol is mannitol and the surfactant is polysorbate 80.

15. The composition of claim 14, which contains 5-20 mg/ml of mannitol and 0.1-10 mg/ml of polysorbate 80.

16. The formulation of claim 13, which contains an antibody, or antigen-binding portion thereof, which binds human TNFα and is the antibody D2E7 or an antigen binding portion thereof.

17. A liquid aqueous pharmaceutical formulation comprising
(a) 1-150 mg/ml of antibody,
(b) 5-20 mg/ml of mannitol,
(c) 0.1-10 mg/ml of Tween-80, and
(d) a buffer system comprising citrate and/or phosphate, with a pH of 4 to 8.

18. The formulation of claim 17, wherein the pH is selected from the group consisting of between about 4.5 to about 6.0, between about 4.8 to about 5.5, and between about 5.0 to about 5.2.

19. The liquid aqueous pharmaceutical formulation of claim 17, which contains
(a) about 50 mg/ml of antibody,
(b) about 12 mg/ml of mannitol,
(c) about 1 mg/ml of Tween-80, and

(d) a buffer system comprising citrate and/or phosphate with a pH of about 4 to about 8.

20. The formulation of claim 17, wherein the buffer system comprises
(a) about 1.3 mg/ml of citric acid,
(b) about 0.3 mg/ml of sodium citrate,
(c) about 1.5 mg/ml of disodium phosphate dihydrate,
(d) about 0.9 mg/ml of sodium dihydrogen phosphate dihydrate, and
(e) about 6.2 mg/ml of sodium chloride.

21. The formulation of claim 19, wherein the antibody is directed to TNFα.

22. The formulation of claim 19, wherein the antibody, or antigen-binding portion thereof, binds human TNFα and is the antibody D2E7 or an antigen binding portion thereof.

23. The formulation of claim 22, which is administered to a subject suffering from a disorder in which TNFα activity is detrimental such that TNFα activity in the subject is inhibited.